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ORIGINAL ARTICLE

International Consensus Guidelines parameters for the prediction of malignancy in intraductal papillary mucinous neoplasm are not properly weighted and are not cumulative

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Abstract

Background: The International Consensus Guidelines (ICG) stratify risk for malignancy in patients with intraductal papillary mucinous neoplasm (IPMN) into three progressive categories according to whether patients show 'no criteria', 'worrisome features' (WFs) or 'high-risk stigmata' (HRS).

Objectives: This study was conducted to test the hypothesis that type (clinical versus radiological) and quantity of ICG WFs and HRS carry unequal weight and are not cumulative in the prediction of risk for malignancy or invasiveness in IPMN.

Methods: A retrospective review of a prospectively maintained database of patients who underwent surgical resection for IPMN at a single, university-based medical centre during 1992–2012 was performed. Differences that achieved a *P*-value of <0.05 were considered significant.

Results: Of 362 patients, 340 were eligible for entry into the study and were categorized as demonstrating no criteria ($n = 70$), WFs ($n = 185$) or HRS ($n = 85$). Patients in the WFs group had higher rates of malignant and invasive IPMN than those in the no-criteria group [26.5% versus 4.3% ($P < 0.0001$) and 15.7% versus 4.3% ($P = 0.02$), respectively]. Patients in the HRS group had higher rates of malignant and invasive IPMN than those in the WFs group [56.5% versus 26.5% ($P = 0.0001$) and 42.4% versus 15.7% ($P = 0.0001$), respectively]. When radiological parameters only were considered for WFs versus HRS, no difference was found in rates of malignant or invasive IPMN. By contrast, when clinical parameters only were considered, patients in the HRS group had higher rates of malignant or invasive IPMN [66.7% versus 8.1% ($P = 0.04$) and 66.7% versus 2.7% ($P = 0.01$), respectively]. There was no stepwise increase in rates of malignant or invasive IPMN with the number of WFs. However, patients with only one WF had a lower risk for malignancy than patients with two or more WFs.

Conclusions: The type and quantity of ICG WFs and HRS carry unequal weight and are not cumulative in the prediction of risk for malignancy or invasiveness in IPMN.

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Introduction

Intraductal papillary mucinous neoplasm (IPMN) was first described by Ohashi *et al.* in 1982[1] in a series of four mucinous neoplasms of the pancreas with pancreatic ductal ectasia. It was then considered an unusual pancreatic entity. Today, it is believed to account for up to 70% of all cystic neoplasms of the pancreas and is the lead indication for pancreatic resection for pancreatic cystic tumours (10–20% of all pancreatectomies).[2] The reasons for the 'IPMN epidemic' are unknown, but it is likely to reflect increased awareness and better detection with improved imaging

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resolution. Because of its increased recognition, the World Health Organization (WHO) established criteria in 1996 to classify and distinguish IPMN from other mucin-producing cystic neoplasms.[3] Similarly, physicians, especially surgeons, felt the urge to gather and discuss the management of this rather new entity. In 2006, the working group of the International Association of Pancreatology proposed international consensus guidelines on IPMN (Sendai Consensus Guidelines),[4] which were revised and updated in 2012.[5]

The precancerous nature of IPMN is now widely accepted to imply a sequence of progression to malignancy from low-grade to high-grade dysplasia and finally to invasive carcinoma (comparable with the progression to malignancy of colonic polyps).[6,7] The current International Consensus Guidelines[5] established surgical indications for IPMN based on several surgical series in which rates and predictors of malignancy were analysed according to IPMN histological subtype. With a risk for malignant transformation of 40–95%,[8,9] it is recommended that all main duct (MD) IPMN in fit patients are resected. Conversely, with an overall risk for malignant transformation estimated at 6–40%,[9–11] the close surveillance of branch duct (BD) IPMN seems reasonable except if select criteria are present or appear during follow-up. The Sendai criteria for the management of BD-IPMN[4] were replaced in 2012 by three categories of risk for malignancy according to which patients are stratified as showing 'no criteria', 'worrisome features' (WFs) or 'high-risk stigmata' (HRS).[5] A previous study published by Ohtsuka *et al*. in 2012[12] analysed the Sendai criteria and concluded that an increase in the number of predictive factors augmented the sensitivity for predicting the malignant potential of BD-IPMN. Similarly, the current International Consensus Guidelines,[5] with their three categories of factors, seem to imply that there is a linear relationship between the category and risk for malignancy.

The present authors hypothesized that the type (clinical versus radiological) and quantity of the 2012 International Consensus Guidelines WFs and HRS are of unequal weight and are not cumulative in the prediction of risk for malignancy or invasiveness in IPMN.

Materials and methods

Patient selection

From 1992 to 2012, data for all patients who underwent surgical pancreatic resection for IPMN at Indiana University Hospital were prospectively collected in a database. For the purpose of this study, this database was retrospectively analysed and supplemented with a review of electronic medical records.

Data were compiled and reported in strict compliance with patient confidentiality guidelines as defined by the Indiana University Institutional Review Board.

Parameters assessed

Based on the 2012 International Consensus Guidelines,[5] a total of nine preoperative parameters were assessed and categorized as representing 'no criteria', 'worrisome features' or 'high-risk stigmata'. The two clinical factors were a history of acute pancreatitis and jaundice. Acute pancreatitis was defined according to the Atlanta consensus or its 2012 revision.[13] Acute pancreatitis was diagnosed if two of the following three features were present: abdominal pain consistent with acute pancreatitis; serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal, and characteristic findings of acute pancreatitis on cross-sectional imaging studies.

The seven remaining factors were radiological and were evaluated on preoperative cross-sectional imaging studies (computed tomography or magnetic resonance imaging/magnetic resonance cholangiopancreatography). They included the size of the largest cyst (<3 cm or ≥3 cm) in BD-IPMN and mixed-type (MT) IPMN, the diameter of the main pancreatic duct (<5 mm, 5–9 mm, ≥10 mm), the presence or absence of an enhancing solid component within the cyst, a non-enhancing mural nodule, thickening enhancing cyst walls or an abrupt change in the calibre of the pancreatic duct with distal pancreatic atrophy and lymphadenopathy.

Pathology

The presence of malignancy as defined by the WHO[14] (high-grade dysplasia, formerly carcinoma *in situ* and invasive carcinoma) and the degree of dysplasia in non-malignant lesions (low-grade and moderate-grade dysplasia) were assessed on final pathology of the surgical specimen. All pathological specimens were reviewed by staff pathologists to confirm the diagnosis of IPMN. Histology was consistent with IPMN if it showed an intraductal proliferation of tall, columnar, mucin-producing cells, arising from the main pancreatic duct and/or a branch duct, with or without papillary projections, and without ovarian-type stroma. Intraductal papillary mucinous neoplasms were also classified into BD-IPMN, MD-IPMN or MT-IPMN based on gross and microscopic histological findings.[5,15,16] For the purpose of the present study, mixed-type variants were considered as MD-IPMN because of the main pancreatic duct involvement.

Exclusion criteria

Patients for whom pathological data were incomplete or whose final pathological diagnosis was not consistent with IPMN were excluded from this study. Patients were also excluded if documentation for all the features described in the 2012 International Consensus Guidelines was not available.

Statistical analysis

Data were recorded using Microsoft Excel 2011 (Microsoft, Inc., Redmond, WA, USA) and analysed with GraphPad Prism Version 5.0 (GraphPad Software, Inc., La Jolla, CA, USA). Descriptive statistics of continuous data included the mean, median, standard error (SE), range and percentage. For subgroup comparisons on categorical data, proportions were compared with Fisher's exact

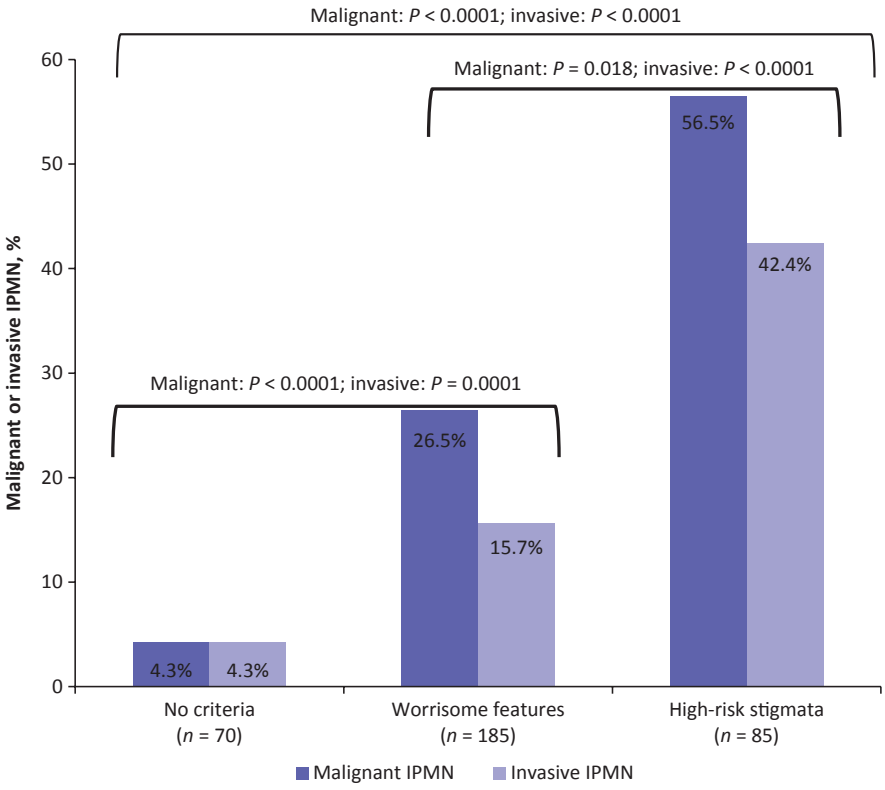

Figure 1 Risk for malignancy and invasiveness in intraductal papillary mucinous neoplasm (IPMN) according to the categories in the 2012 International Consensus Guidelines. All *P*-values are significant at < 0.05

test as appropriate. Student's *t*-test was used to compare continuous variables. A *P*-value of < 0.05 was accepted as indicating statistical significance.

Results

Patient population

Between 1992 and 2012, 362 patients were diagnosed with IPMN and subsequently underwent surgical resection. Complete data were available for 340 patients, who were included in this study. Their mean ± SE age was 68.2 ± 11.6 years (range: 31–93 years) and the gender ratio of the sample was 0.94 (165 men and 175 women).

International Consensus Guidelines parameters

Based on the 2012 International Consensus Guidelines, 'worrisome features' (WFs) included a history of acute pancreatitis, a cyst size of ≥3 cm, a main pancreatic duct diameter of 5–9 mm, a non-enhancing mural nodule and lymphadenopathy. 'High-risk stigmata' (HRS) included jaundice, the presence of an enhancing solid component within the cyst or a main pancreatic duct diameter of ≥10 mm. In the present population, 70 patients (20.6%) were diagnosed as showing 'no criteria', 185 (54.4%) with WFs and 85 (25.0%) with HRS.

Contrary to the Sendai criteria, which described predictors of malignancy for BD-IPMN only, the 2012 International Consensus Guidelines algorithm analyses IPMNs altogether, considering main duct dilation as a WF or HRS (depending on the diameter of the main duct). Therefore, the present authors decided to analyse both BD-IPMN and MD/MT-IPMN together in the way presented in the revised guidelines. The analysis of MD/MT-IPMN alone raised the issue of bias as main duct dilation itself already represents a WF or HRS; hence, in order to achieve a thorough analysis, BD-IPMN was also analysed separately.

Pathology

Pathology was consistent with BD-IPMN and MD-IPMN (or MT-IPMN) in 170 patients (50.0%) and 170 patients (50.0%), respectively. On pathology review, 100 IPMNs (29.4%) were classified as malignant, 32 (9.4%) as high-grade dysplasia and 68 (20.0%) as invasive carcinoma. The remaining 240 benign IPMNs (70.6%) included 152 low-grade dysplasia IPMN (44.7%) and 88 moderate-grade dysplasia IPMN (25.9%).

Progression in risk for malignancy or invasiveness across the three categories

There was a significant increase in the rates of malignant and invasive IPMN with the category of factors, as shown in Fig. 1.

Table 1 Importance of the subtypes of 'worrisome features' (WFs) and 'high-risk stigmata' (HRS) to the prediction of risk for malignancy and invasiveness in intraductal papillary mucinous neoplasms

Criteria subtype	Malignancy	*P*-value	Invasiveness	*P*-value
Radiological WFs (n = 97)	30 (30.9%)	0.66	20 (20.6%)	1
Radiological HRS (n = 30)	11 (36.7%)		6 (20%)	
Clinical WFs (n = 37)	3 (8.1%)	0.036[a]	1 (2.7%)	0.011[a]
Clinical HRS (n = 3)	2 (66.7%)		2 (66.7%)	

[a]Significant *P*-value ($P < 0.05$).

Patients with no criteria, with WFs and with HRS had risks for malignancy of 4.3%, 26.5% and 56.5%, respectively. Similarly, rates of invasive IPMN were 4.3%, 15.7% and 42.4%, respectively, in the same three categories.

Importance of each factor for the prediction of risk for malignancy or invasiveness

A total of 97 (52.4%) of the 185 patients with WFs had radiological WFs. Thirty (35.3%) of the 85 patients with HRS had radiological HRS. However, 37 (20.0%) of the WFs patients had clinical WFs and three (3.5%) of the HRS patients had clinical HRS. When radiological parameters only were considered, no difference in rates of malignant or invasive IPMN was found between patients with WFs and HRS, respectively. By contrast, when only clinical factors were taken into account, patients with HRS had higher rates of malignant and invasive lesions (8.1% versus 66.7% and 2.7% versus 66.7%; $P = 0.036$ and $P = 0.011$, respectively). These results are summarized in Table 1.

Influence of the number of factors on the prediction of risk for malignancy or invasiveness

Of the 185 patients with WFs, 104 (56.2%) patients had one WF, 70 (37.8%) had two WFs and 11 (5.9%) had three or more WFs. Of the 85 patients with HRS, 80 (94.1%) had one HRS and five (5.9%) had two. A comparison of risk for malignancy and invasiveness in patients with one versus two, two versus three and, finally, one versus three WFs is displayed in Table 2. The only statistically significant difference was found for malignant IPMN and pertained to the difference between patients with one or two WFs, respectively. To further analyse this association, patients with only one WF were compared with patients with two or more WFs. Patients with only one WF were found to have a significantly lower rate of malignant IPMN (15.4% versus 40.7%; $P = 0.0002$), suggesting an additive risk when two or more WFs were present. When only radiological factors were considered (Table 3), similar overall results became apparent and a similar additive risk in patients with two or more radiological WFs emerged (19.4% versus 58.6%; $P = 0.0006$).

When patients with one HRS were compared with patients with two or more, a trend toward greater rates of malignant and invasive IPMN emerged with more HRS, although it did not reach statistical significance [malignancy: 53.8% versus 100% ($P = 0.065$); invasiveness: 40.0% versus 80.0% ($P = 0.16$)].

Influence of the association of HRS and WFs

The presence of at least one HRS causes a patient to fall into the HRS category, regardless of the presence of WFs. However, an analysis to establish whether the association of WFs and HRS was cumulative was conducted. Among the 85 patients in the HRS category, 15 (17.6%) had HRS only, whereas 70 (82.4%) had both WFs and HRS. Interestingly, the presence of HRS only was associated with higher rates of malignant (86.7% versus 50.0%; $P = 0.01$) and invasive IPMN (93.3% versus 34.3%; $P = 0.0007$).

Separate analysis of BD-IPMN

Similar results were found for BD-IPMN alone. There was a stepwise increase in risk for malignancy and invasiveness across patients with no criteria, WFs and HRS [5.3%, 12.2% and 43.5%, respectively ($P < 0.0001$) for malignancy; 5.3%, 6.7% and 34.8%, respectively ($P = 0.0015$) for invasiveness]. There was no difference in risk for malignancy and invasiveness between radiological WFs and radiological HRS. Conversely, clinical HRS were associated with a greater rate of malignant IPMN than clinical WFs (100% versus 4%; $P = 0.008$). There was no stepwise increase in rates of malignant or invasive IPMN with the number of WFs. However, patients with only one WF had a lower risk for malignancy than patients with two or more WFs (6.9% versus 21.9%; $P = 0.048$).

Discussion

The 2012 International Consensus Guidelines[5] classify patients into three categories of risk based on several features that are associated with malignancy and invasiveness. The present study analysed the influence of the subtype and numbers of those factors on the prediction of risk for malignancy and invasiveness in IPMN. According to the present results, the type and quantity of WFs and HRS carry unequal weight. Clinical parameters, in general, are more predictive and should carry more weight in surgical decision making. 'Worrisome features' and especially radiological WFs are not cumulative in risk prediction as there is no stepwise increase in rates of malignant or invasive IPMN with the number of WFs. However, patients with only one WF should be considered at lower risk for malignancy than patients with two or more WFs. Finally, the addition of WFs to HRS did not increase rates of malignant or invasive IPMN in comparison with HRS alone.

Invasive IPMN has a better prognosis than classic pancreatic adenocarcinoma in patients matched by T1 or N0 status, or by the subtype of colloid carcinoma. However, in the other conditions (T2–T4, N1 and other pathological subtypes), invasive IPMN is associated with a poor prognosis similar to that of classic pancreatic adenocarcinoma,[17,18] with 5-year survival of 4–6%.[19] Because of this potential for malignancy, IPMNs have been resected in all

Table 2 Influence of the number of 'worrisome features' (WFs) on the prediction of risk for malignancy and invasiveness in intraductal papillary mucinous neoplasms (IPMN)

Number of WFs	Malignant IPMN	*P*-value			Invasive IPMN	*P*-value		
1 (n = 104)	16 (15.4%)			0.098	11 (10.6%)			0.13
2 (n = 70)	29 (41.4%)	<0.0002[a]			15 (21.4%)	0.054		
≥3 (n = 11)	4 (36.4%)		1		3 (27.2%)		0.70	

[a]Significant *P*-value ($P < 0.05$).

Table 3 Influence of the number of radiological 'worrisome features' (WFs) on the prediction of risk for malignancy and invasiveness in intraductal papillary mucinous neoplasms (IPMN)

Number of radiological WFs	Malignant IPMN	*P*-value			Invasive IPMN	*P*-value		
1 (n = 67)	13 (19.4%)			0.37	10 (14.9%)			0.29
2 (n = 28)	16 (57.1%)	<0.0005[a]			9 (32.1%)	0.089		
≥3 (n = 2)	1 (50.0%)		1		1 (50.0%)		1	

[a]Significant *P*-value ($P < 0.05$).

patients for decades. As a result of the increased incidental detection of lesions in cross-sectional imaging studies[20] and the benign pathology of the majority of resected IPMNs, this approach has had to change.[21,22] In 2006, the International Association of Pancreatology proposed guidelines for the management of IPMN (the Sendai criteria).[4] These first guidelines proved to be highly sensitive (80–97%) but non-specific (25–30%) and to have a low positive predictive value (14–22%),[23–25] which led to the suboptimal detection of malignant IPMN and the over-treatment of minimally or asymptomatic patients with non-malignant disease. Subsequently, the guidelines were revisited and updated in 2012. The new 2012 International Consensus Guidelines[5] have since been widely adopted in the surgical decision-making process.

The current study is subject to several limitations that must be discussed here. It is a retrospective study covering over 20 years spanning several periods of IPMN management based on different protocols at this institution (according to indications for surgical resection based on the presence of IPMN before 2000, the Sendai criteria after 2006, and the 2012 guidelines more recently).

The present sample represents a surgical series and thus it cannot be concluded whether these results can be generalized to a surveillance population. In view of this selection bias, it was decided that the study should include only patients who had been operated on in order to ensure a confirmed diagnosis of IPMN and of malignancy or invasiveness according to the final pathology of the resected specimen, which represents the reference standard for diagnosis. A mixed series (both surveillance and surgery) would have shown the true incidence of WFs and HRS in patients with IPMN, but would have been less than optimal in assessing the true risks for malignancy and invasiveness. If assessed on cross-sectional imaging, signs of malignancy (vascular encasement, metastases, peritoneal carcinomatosis) imply late-stage disease. The assessment of malignancy on cytopathology also presents several drawbacks as the positive predictive value of this method is excellent (near 100%), but the absence of high-grade atypical cells or degenerated cells does not exclude the possibility of malignancy.

To the present authors' knowledge, to date no study has analysed the roles of both the number and type of criteria used in the prediction of risk for malignancy. Only one study has analysed the impact of the number of criteria. Despite being published in 2012, a series by Ohtsuka *et al.*[12] analysed the Sendai criteria and concluded that an increase in the number of predictive factors augmented the sensitivity of predictions of the malignant potential of BD-IPMN. Since the International Consensus Guidelines were updated, multiple studies have validated the impacts of HRS and WFs in IPMN risk prediction. A recent meta-analysis of 5788 patients suggested that the contributions of those criteria to the progression of IPMN to malignancy were unequal based on differential odds ratios (ORs).[26] In this meta-analysis, cyst size was associated with the highest OR of 62, whereas mural nodule and main duct involvement generated ORs of 9 and 7, respectively.[26] Conversely, a recent German study concluded that even small IPMNs without criteria suspicious for progression demonstrated a rate of malignancy of 24.6%.[27] Based on their controversial results, this latter team advocate a more liberal policy in IPMN, even in lesions that do not meet the guidelines criteria. However, this study also based its analysis on the Sendai criteria rather than on the updated WFs and HRS.[27]

These guidelines are based on results from large series and general populations and may not be applicable on an individual-patient basis. However, predicting the risk for malignancy or invasiveness in each patient is more important as a patient with a suspicious lesion will undergo standard oncological pancreatectomy with lymphadenectomy, whereas a patient with supposedly benign lesion(s) can undergo organ-sparing pancreatectomy or even close surveillance. This decision presents several consequences. Firstly, despite recent progress in pancreatic surgery, pancreatic resection is still associated with mortality rates of up to 5% and morbidity rates of 20–40%.[28,29] Secondly, a cost-effectiveness

analysis published in 2010[30] concluded that surgery was associated with a global incremental cost of more than US$20 000 dollars over a surveillance strategy, which represents an increased expense that is not justified in benign lesions. Based on those limitations, the Memorial Sloan – Kettering Cancer Center attempted to develop a preoperative nomogram in which clinical and radiological criteria were combined into one system.[31] On the basis of this latter study and the present results, it would appear that a malignancy score may be more accurate than standard risk categories as it will reflect the number and weight of each feature.

The preoperative prediction of malignancy and invasiveness in IPMN has been widely studied and has been summarized in the 2012 International Consensus Guidelines,[5] which represent an improvement on the 2006 Sendai criteria.[4] However, the new algorithm remains suboptimal in predicting risk for malignancy and in maintaining a balance between under- and over-treatment because it considers every parameter to have an equal association with risk for malignancy, which the present study has proved to be incorrect. A scoring system based on a large series and including multivariate analysis and the calculation of ORs may prove more adequate to accurately assess risk for malignancy or invasiveness in IPMN.

Conflicts of interest

None declared.

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